

## STATE-OF-THE-ART PAPER

# Evaluation and Management of the Cardiac Amyloidosis

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Cardiac amyloidosis describes clinically significant involvement of the heart by amyloid deposition, which may or may not be associated with involvement of other organs. The purpose of this review is to summarize the current state of evidence for the effective evaluation and management of cardiac amyloidosis. Acquired systemic amyloidosis occurs in more than 10 per million person-years in the U.S. population. Although no single noninvasive test or abnormality is pathognomonic of cardiac amyloid, case-control studies indicate that echocardiographic evidence of left ventricular wall thickening, biatrial enlargement, and increased echogenicity in conjunction with reduced electrocardiographic voltages is strongly suggestive of cardiac amyloidosis. Furthermore, newer echocardiographic techniques such as strain and strain rate imaging can demonstrate impairment in longitudinal function before ejection fraction becomes abnormal. Recent observational studies also suggest that cardiovascular magnetic resonance imaging yields characteristic findings in amyloidosis, offering promise for the early detection of cardiac involvement, and the presence of detectable cardiac troponin and elevated B-type natriuretic peptide in serum of affected patients portends an adverse prognosis. Management strategies for cardiac amyloid are largely based on nonrandomized single-center studies. One of the few published randomized studies shows the superiority of oral prednisolone and melphalan compared with colchicine in systemic AL amyloidosis. Intermediate-dose infusional chemotherapy regimes (such as vincristine, adriamycin, and dexamethasone) and high-dose chemotherapy with peripheral stem cell rescue have been used widely, but treatment-related mortality remains substantial with chemotherapy. Recent studies also indicate promising strategies to stabilize the native structures of amyloidogenic proteins; inhibit fibril formation; and disrupt established deposits using antibodies, synthetic peptides, and small-molecule drugs. (J Am Coll Cardiol 2007;50:2101–10) © 2007 by the American College of Cardiology Foundation

Amyloidosis is a clinical disorder caused by extracellular deposition of insoluble abnormal fibrils, derived from aggregation of misfolded normally soluble protein (1,2). About 20 different unrelated proteins, which share a pathognomonic ultrastructure, are known to form amyloid fibrils in vivo (3). Systemic amyloidosis, in which amyloid deposits are present in the viscera, blood vessel walls, and connective tissues, is usually fatal and is the cause of about 1 per 1,000 deaths in developed countries. There are also various localized forms of amyloidosis in which the deposits are confined to specific foci or to a particular organ or tissue. “Cardiac amyloidosis” is used here to describe involvement of the heart by amyloid deposition, whether as part of systemic amyloidosis (as is most commonly the case) or as a localized phenomenon.

Variation in nomenclature, and the fact that there are several types of amyloid, each with its unique features and treatment, can result in underdiagnosis and errors in patient management. The purpose of this review is to summarize the current state of evidence for the effective clinical evaluation and management of cardiac amyloidosis.

## Evidence Acquisition

We performed a systematic review of peer-reviewed publications that were identified through searches of MEDLINE and the Cochrane Database from 1980 to June 2007. Besides cardiac amyloidosis and plasma cell dyscrasia, we searched all drugs used to treat plasma cell dyscrasia. Keywords were used alone and with the modifiers of *diagnosis, treatment, clinical effects, troponin, electrocardiography, echocardiography, and magnetic resonance imaging*. Bibliographies from these references were reviewed, as were additional articles identified by content experts. Criteria used for study selection included study design, English language, relevance to clinicians, and validity based on venue of publication.

**Classification.** Acquired systemic amyloidosis occurs in more than 10 per million person-years in the U.S. popula-

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**Abbreviations  
and Acronyms****CMR** = cardiovascular  
magnetic resonance  
imaging**ECG** = electrocardiogram/  
electrocardiographic**LV** = left ventricular**SAA** = serum amyloid A  
protein**SAP** = serum amyloid P  
component**SSA** = senile systemic  
amyloidosis**TTR** = transthyretin

tion (4), is the cause of death in about 1 in 1,000 of the British population, and is probably much underdiagnosed in the elderly population. Systemic AL amyloidosis is the most serious and commonly diagnosed form, with 2,000 to 2,500 new cases annually in the U.S. (5).

**Systemic AA amyloidosis.** Formerly known as secondary amyloidosis, systemic AA amyloidosis is a complication of chronic inflammatory conditions, or indeed, any disorder associated with a sustained acute-phase response in which there is mark-

edly increased production of serum amyloid A protein (SAA). Renal disease dominates the clinical picture in AA amyloidosis, and the condition almost always presents with proteinuria and renal failure. Regression of AA amyloid following suppression of SAA production may lead to reversal of organ dysfunction (6). Clinically significant involvement of the heart is very rare (7).

**Systemic AL amyloidosis.** Previously known as primary amyloidosis, systemic AL amyloidosis is the most commonly diagnosed form of clinical amyloid disease in developed countries. The AL fibrils are derived from monoclonal immunoglobulin light chains and consist of the whole or part of the variable (VL) domain. Almost any B-cell dyscrasia, including myeloma, lymphomas, and macroglobulinaemia, may be complicated by AL amyloidosis, but more than 80% of cases are associated with subtle and otherwise “benign” monoclonal gammopathies. Multiorgan infiltration is typical. It occurs equally in men and women, usually over the age of 50 years but as early as the third decade. The heart is affected pathologically in up to 90% of AL patients, in 50% of whom diastolic heart failure with physical signs of right heart failure is a presenting feature. Conversely, <5% of patients with AL amyloidosis involving the heart have clinically isolated cardiac disease (8). Clinical evaluation of suspected cardiac AL amyloid includes screening for syncope (9), dizziness, postural hypotension, easy bruising (10), painful sensory polyneuropathy (10% to 20% of patients), and carpal tunnel syndrome (20%) (11), as well as major visceral involvement of the liver and kidneys. The presence of both periorbital purpura and macroglossia has low sensitivity (10% to 20%) but is highly specific for the presence of disease (12). Death in more than one-half of these patients is due either to heart failure or arrhythmia.

*Hereditary systemic amyloidosis* is caused by deposition of amyloid fibrils derived from genetic variants of transthyretin (TTR) (13), apolipoprotein A-I, lysozyme (14), or fibrinogen alpha-chain and other extremely rare variants. Clinical syndromes include cardiomyopathy, nephropathy, or neuropathy (15), though the heart is most prominently involved

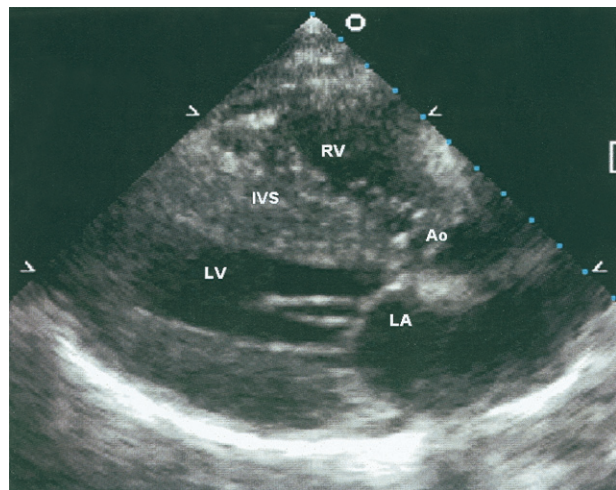
in variant TTR type, which is associated with more than 100 different TTR mutations, most often with associated neuropathy. This entity is not rare; indeed, the amyloidogenic TTR Val122Ile variant is present in 4% of African Americans, and 23% of African Americans with cardiac amyloidosis have this variant (16).

*Senile systemic amyloidosis (SSA)* is caused by deposition of amyloid fibrils derived from normal wild-type transthyretin and almost always presents as a slowly progressive, infiltrative amyloid cardiomyopathy. Senile systemic amyloidosis is exceptionally rare in those younger than 60 years of age, but its prevalence ranges from 25% to 36% in those older than 80 years of age (17,18). There is a large male predominance, and senile systemic amyloidosis has a major predilection for the heart (19,20). Patients usually present with congestive heart failure, with carpal tunnel syndrome being the only common accompanying extracardiac manifestation. Normal-voltage electrocardiogram (ECG) with a left anterior fascicular block and thickened left ventricular (LV) walls on echocardiography are characteristic. Despite the older age and greater myocardial infiltration, the median SSA survival of 75 months is greater than for AL amyloidosis (21). The slowly progressive nature, despite greater myocardial infiltration, distinguishes SSA from AL amyloidosis. Diagnosis is often surmised but can be achieved definitively by the demonstration of TTR type amyloid on either cardiac or, occasionally, other (e.g., rectal) biopsy, along with absence of mutations in the TTR gene. There is no specific therapy available, and death is usually due to congestive heart failure or arrhythmias.

## Noninvasive Evaluation of Cardiac Amyloidosis

Echocardiography can show several features that are suggestive of cardiac amyloidosis (Fig. 1), though the classical features are commonly present only in the later stages of disease (22,23), and there is a wide spectrum of echocardiographic findings. Echocardiography cannot confirm diagnosis in isolation, and the images should be interpreted in the context of the clinical picture and other investigations. The AA amyloid very rarely affects the heart, and the common types that do, such as AL and variant/wild-type TTR types, cannot be distinguished by echocardiogram alone. Although very rare indeed, hereditary apolipoprotein A-I amyloidosis sometimes involves the heart, producing similar echocardiographic abnormalities.

The most common echocardiographic feature is thickening of the LV wall, particularly in the absence of hypertension. (22,24–28) This is often referred to incorrectly as “hypertrophy” because the pathological process is infiltration, not myocyte hypertrophy. This feature has poor specificity for amyloidosis because of its occurrence with other conditions, such as hypertensive heart disease, hypertrophic cardiomyopathy, and other infiltrative cardiac diseases (glycogen storage diseases, sarcoidosis, hemochromatosis). The combination of increased LV mass in the



**Figure 1** 2D Echocardiographic Image (Parasternal Long-Axis View) From a Patient With AL Cardiac Amyloidosis

Two-dimensional (2D) echocardiographic image (parasternal long-axis view) from a patient with AL cardiac amyloidosis showing normal biventricular dimensions, granular “sparkling” ventricular wall appearance, concentric left ventricular wall thickening, and thickened mitral valve leaflets suggesting infiltration. Ao = aorta; IVS = interventricular septum; LA = left atrium; LV = left ventricle; RV = right ventricle.

absence of high ECG voltages may be more specific for infiltrative diseases, of which amyloid is the most common (24,29). High sensitivity (72% to 79%) and specificity (91% to 100%) have been reported for this combination (27,29), though some study sizes are small and may be influenced by referral bias. The Dubrey et al. study (8) did not include a comparison group but showed low ECG voltages in 70% to 74% of amyloid patients with mildly increased LV wall thickness ( $>1.1$  cm).

Increased echogenicity of the myocardium, particularly with a granular or “sparkling” appearance, has been reported in several studies (10,27,28,30,31). This can occur in other causes of LV hypertrophy, however (10,27,30), and although high specificity rates are quoted (71% to 81%) (10,27), the populations studied were those referred with suspected amyloid, and this specificity may not be reflective of real-life practice. Moreover, sensitivity tends to be low, with this pattern seen in 26% to 36% of cardiac amyloid cases (27,32–34), apart from a single study suggesting a sensitivity of 87% (10). It should be noted that this granular pattern applies only to standard echocardiographic imaging, without tissue harmonics being applied, as this increases myocardial echogenicity in general. Newer echocardiographic image processing techniques may also reduce the granular appearance. Thus, although increased echogenicity is common in amyloid, its usefulness as a discriminating factor is limited.

Reduced systolic function, as measured by low ejection fraction or poor wall thickening, is uncommon until the more severe stages of disease and can be absent in up to 75%

of cases (12,23,25–27,33). Diastolic dysfunction is the hallmark, and may be present in all patients, though its identification can be difficult with standard techniques, with 21% to 88% of patients showing a restrictive pattern on Doppler mitral inflow assessment (25,35,36). The variable prevalence of diastolic dysfunction may also be related to the severity of disease in the group studied, as the likelihood of a restrictive physiological pattern increases with the severity of disease (25,36). Tissue Doppler imaging has shown reduced diastolic velocities in both early and late cardiac amyloid (22,37), so even early diastolic dysfunction could be identified (when wall thickening is minimal), though distinguishing individuals with and without heart failure is more difficult, with significant overlap between the groups (37). It is, however, good at distinguishing amyloid and other restrictive cardiomyopathies from constrictive pericarditis, with a mitral annular diastolic velocity ( $E'$ )  $<8$  cm/s a good discriminator for restrictive physiology (38). Finally, although diastolic dysfunction is commonly (if not uniformly) present, it should be remembered that diastolic dysfunction is not specific for amyloidosis and should be taken together with the clinical picture and other investigations.

Other features of cardiac amyloid include thickened valves and a small pericardial effusion, and although these have been described in 40% to 60% of patients (28,33), they tend to be present in more advanced disease (12). Again, it should be remembered that these are highly selected groups in the studies. Similarly, bilaterally enlarged atria have been described in 27% to 50% (27,28,33) but are not specific for amyloid (27). A thickened interatrial septum has been shown in a minority of patients (28), and a study by Falk et al. (30) showed it to be specific for amyloid in the later stages of the disease, with 100% specificity. This was in a relatively small group of patients, however, and has not been reproduced subsequently. Other parameters such as atrial strain and ventricular strain rate imaging show mean differences between amyloid groups with and without heart failure (38,39), but the considerable overlap in values between groups limits the clinical application of these techniques.

In summary, there are many echocardiographic features common in amyloid, though none are highly specific individually, and a combination of several is helpful in achieving a diagnosis. An echocardiogram demonstrating marked LV wall thickening, biatrial enlargement, thickened valve leaflets, and a pericardial effusion in the context of reduced ECG voltages is highly persuasive of cardiac amyloid. If either a thickened interatrial septum or a granular highly echogenic myocardium is also present, this makes the diagnosis even more likely (30). Combining features has been shown to be good at differentiating cardiac amyloid from other diagnoses (40,41), though the most useful method is to combine these with the wider clinical findings.

**Electrocardiography.** Systematic study of ECG findings in biopsy-confirmed cardiac amyloidosis is relatively sparse.



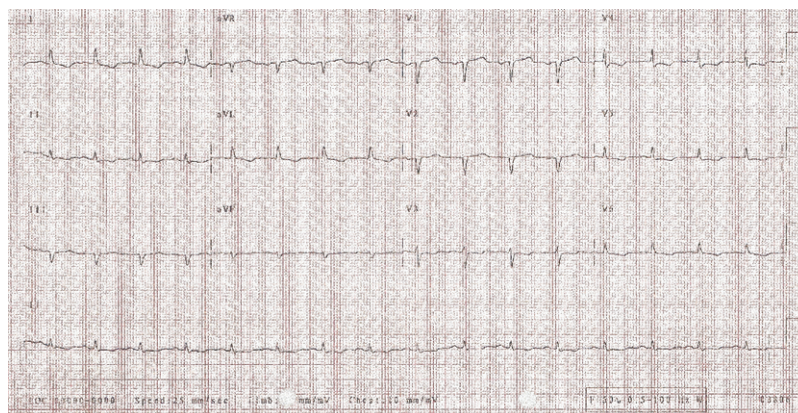
Murtagh et al. (42) from the Mayo Clinic provide the largest report to date of ECG findings in a population of patients with AL amyloidosis and biopsy-proven cardiac involvement. In 127 patients, they found that low ECG voltage (presence of QRS voltage amplitude  $\leq 0.5$  mV in all limb leads or  $\leq 1$  mV in all precordial leads) (Fig. 2) was present in 46% of patients, and a pseudo-infarct pattern (i.e., no infarct actually evident on echocardiography) was present in 47% of patients. The pseudo-infarct patterns were anterior (36%), inferior (12%), and lateral (14%). Both low ECG voltage and pseudo-infarct pattern were present in 25% of patients. There was a moderate correlation between the presence of low voltage and pericardial effusion but no correlation between voltage and the ejection fraction. Atrial fibrillation and flutter was the most common arrhythmia. It was present in 25% of patients with LV hypertrophy, whereas 7% of patients without LV hypertrophy were identified as having atrial fibrillation (42). None of the electrocardiographic variables correlated with survival. Though low voltage and pseudo-infarct patterns are common, increased voltages suggesting LV hypertrophy are occasionally found in amyloid. These findings are similar to an earlier report in 196 patients (with high clinical suspicion of cardiac amyloid) by Rahman et al. (27), who noted low ECG voltage in 56% and pseudo-infarct pattern in 60% of patients who were subsequently confirmed to have cardiac amyloid. In multivariate logistic regression analysis, a combination of a low voltage and measures of myocardial thickness produced the best discriminator of cardiac involvement in this study. The investigators found that if low voltage was present on ECG and interventricular septal thickness was  $>1.98$  cm on echocardiography, the diagnosis of cardiac amyloidosis could be made with a sensitivity of 72% and a specificity of 91%. In this model, the positive predictive and negative predictive values were 79% and 88% respectively, although the findings may not be applicable in

the general population given the selective nature of the cohort study (27).

Signal-averaged ECG is often abnormal (delayed myocardial activation or “late potentials”) in patients with AL amyloidosis. Dubrey et al. (43) found that late potentials were more frequent in patients with echocardiographic evidence of cardiac amyloidosis (31%) compared with patients with normal echocardiograms (9%,  $p < 0.003$ ) (43). Furthermore, abnormal signal-averaged electrocardiograms were also independently predictive of sudden death in the subgroup of patients with an abnormal echocardiogram ( $p < 0.05$ ). Reduced heart rate variability on 24-h ECG monitoring has been found to predict short-term mortality in both AA and AL amyloidosis in a small case series (44) and probably represents autonomic dysfunction.

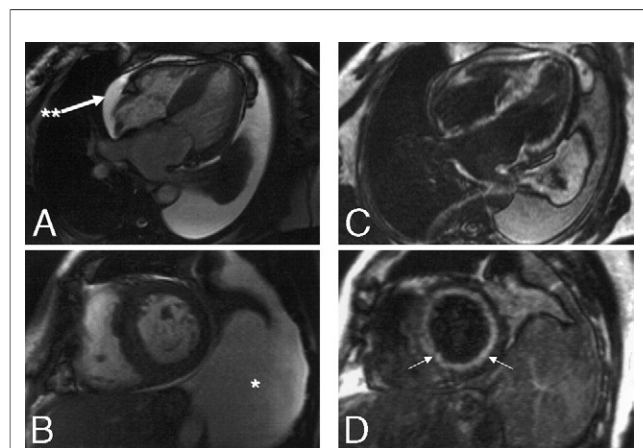
**Cardiovascular magnetic resonance imaging (CMR).** A strength of CMR using late gadolinium enhancement technique is the ability to “phenotype” various forms of cardiomyopathy with high spatial resolution and reproducibility (45,46). Maceira et al. (47) studied 29 patients with systemic amyloidosis and 16 hypertensive controls using gadolinium-enhanced CMR. Amyloidosis was associated with qualitative global and subendocardial gadolinium enhancement of the myocardium (Fig. 3). Subendocardial longitudinal relaxation time (T1) in amyloid patients was shorter than in control subjects and was correlated with markers of increased myocardial amyloid load, such as LV mass, wall thickness, interatrial septal thickness, and diastolic function. Global subendocardial late gadolinium enhancement was found in approximately two-thirds of patients. On the basis of pathological correlates in a patient from this study, the CMR hyperenhancement probably represents interstitial expansion from amyloid infiltration.

Perugini et al. (48) studied an Italian population of patients with histologically proven systemic amyloidosis and echocardiographic diagnosis of cardiac involvement. Gado-



**Figure 2** Typical Appearance of the Electrocardiogram in Cardiac Amyloidosis

There is low voltage with lateral T-wave inversion and poor R-wave progression in the precordial leads.



**Figure 3** End-Diastolic Frames of Cines

Horizontal long-axis (A) and short-axis (B) at the mid-ventricular level, showing pleural (\*) and pericardial effusions (\*\*) and asymmetrical hypertrophy (maximal end-diastolic wall thickness: septum 22 mm, lateral wall 9 mm, wall thickness ratio of 2.6). Corresponding images using the delayed-enhancement magnetic resonance imaging technique: C and D, respectively. The horizontal long-axis image demonstrates global subendocardial hyperenhancement of both ventricles, both atria and the interatrial septum. The short-axis image displays a ring of subendocardial hyperenhancement (arrows).

linium enhancement by CMR was detected in 16 of 21 (76%) patients. In contrast to the study of Maciera et al. (47), where the pattern of late enhancement was global and subendocardial, Perugini et al. (48) reported a much more variable pattern of late enhancement, that could be localized or diffuse, and subendocardial or transmural. Transmural extension of hyperenhancement (i.e., how much of the LV wall thickness was enhanced) within each patient significantly correlated with LV end systolic volume. The number of enhanced segments correlated with LV end-diastolic volume, end-systolic volume, and left atrial size. An especially unique feature of delayed-enhancement magnetic resonance imaging appearances in this population is the blood pool's atypically dark appearance, which reflects the similar myocardial and blood T1 values attributable to high myocardial uptake and fast blood pool washout. Although it is yet to be proved, imaging with a highly reproducible and quantifiable technique such as CMR may help to estimate the prevalence of cardiac involvement in systemic amyloidosis when cardiac morphological changes are not apparent by echocardiography. Screening of subclinical early cardiac involvement may become possible should delayed enhancement prove to have adequate sensitivity in detecting amyloid infiltration. Improved noninvasive surveillance may also aid in the evaluation of new chemotherapeutic agents.

**Radiolabeled serum amyloid P component (SAP) scintigraphy.** Serum amyloid P component is a highly conserved, invariant plasma glycoprotein of the pentraxin family that becomes specifically and highly concentrated in amyloid deposits of all types as a result of its calcium-dependent binding to all types of amyloid fibril. Following intravenous

injection, radiolabeled SAP distributes between the circulating and the amyloid-bound SAP pools in proportion to their size and can then be imaged and quantified (49,50). This safe noninvasive method provides unique information on the diagnosis, distribution, and extent of amyloid deposits throughout the body, and serial scans monitor progress and response to therapy. Serial SAP scans have unequivocally demonstrated that amyloid deposits of all types regress in a proportion of patients when the supply of the respective amyloid fibril precursor protein is sufficiently reduced. Unfortunately, planar SAP scintigraphy is unable to image amyloid in the moving heart.

**Biochemistry.** Cardiac biomarkers are elevated in cardiac AL amyloidosis, often to a degree that seems to be disproportionate to symptoms of congestive heart failure (51). That cardiac troponins are detected is not surprising, as troponin values are invariably associated with pathological evidence of cardiac injury, irrespective of causation (52,53). Myonecrosis and small-vessel ischemia due to amyloid deposit lead to an increase in cardiac troponins (54), whereas diastolic dysfunction and increased genetic expression of natriuretic peptide genes in the amyloid infiltrated ventricles lead to an increase in plasma B-type natriuretic peptide (BNP) levels (55). Troponin T and I and N-terminal (NT)-proBNP levels at diagnosis provide prognostic information in amyloidosis. In the largest series to date, Dispenzieri et al. (56) found that in 261 newly diagnosed patients with cardiac amyloidosis, detectable cardiac troponin I or T conferred a median survival of 6 or 8 months (respectively), compared with 22 or 21 months (respectively) in those without any detectable troponin I/T. Furthermore, their data imply that raised values of serum cardiac troponins may surpass symptomatic congestive heart failure and 2-dimensional echocardiography as predictors for survival.

The role of cardiac biomarkers in monitoring disease progression or response to therapy is still being defined. Curiously, in AL amyloidosis, NT-proBNP values can fall rapidly following effective chemotherapy; a 30% reduction in NT-proBNP levels after 3 doses of chemotherapy has been associated with improved event-free survival, though this did not correlate with objective assessments on the echocardiogram (57). Prognosis with a hematological response following chemotherapy is substantially better than in patients without, and the basis for changes and the true value of serial NT-proBNP measurements in the management of AL amyloidosis are not yet clear.

A new serum immunoglobulin free light chains assay, which can quantify the aberrant circulating amyloidogenic fibril protein precursor with great sensitivity in 85% to 98% of patients with AL amyloidosis, is a major recent advance in the disease (57). This automated immunoassay can serially monitor production of amyloidogenic light chains during chemotherapy (58). A 50% reduction in aberrant serum free light chains following chemotherapy was paralleled by reductions in NT-proBNP and associated with improvement clinically but not in LV wall thickness (57). Further imaging studies with a highly

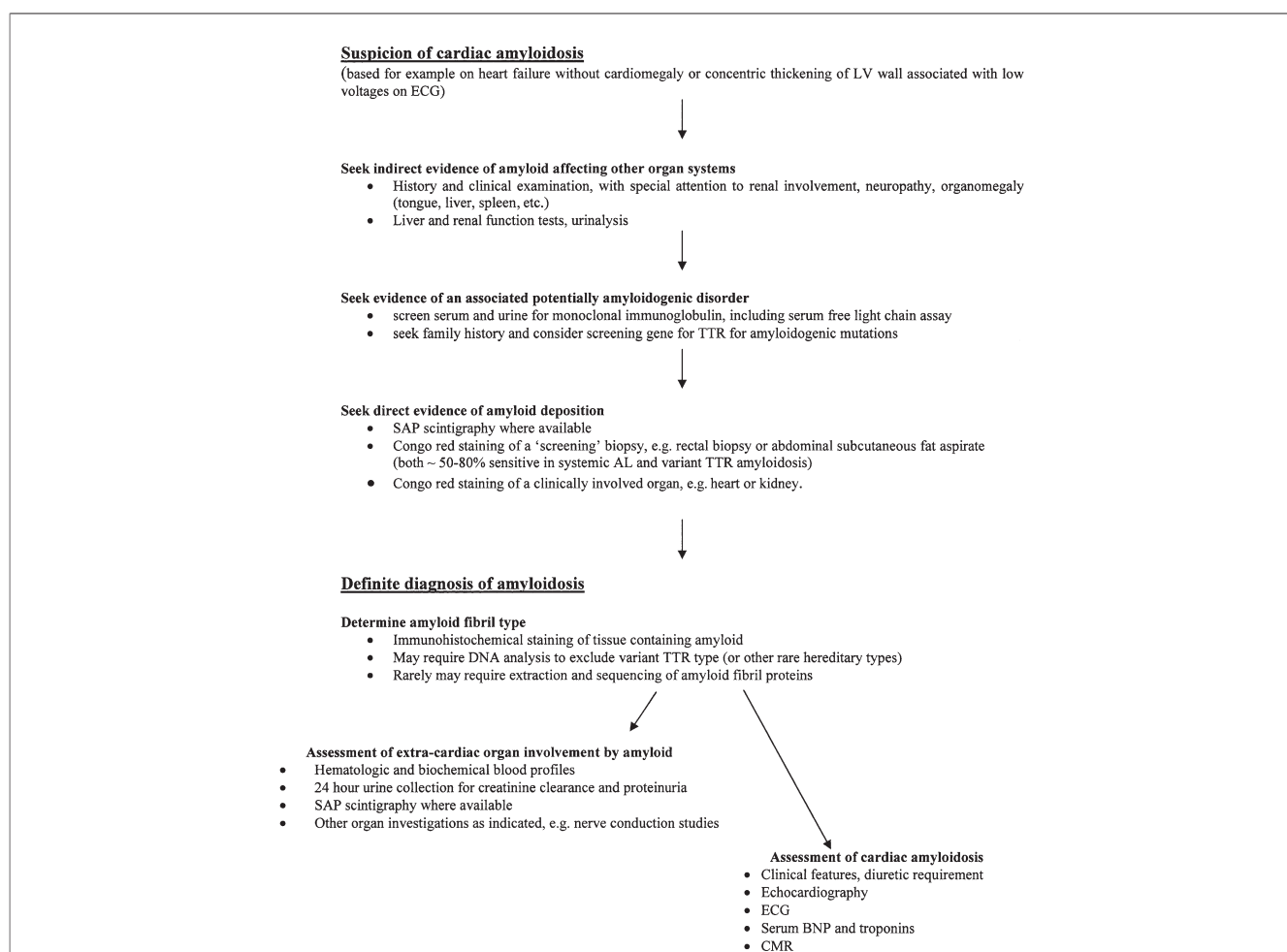
reproducible and quantifiable technique such as CMR may help to define correlations between cardiac function and changes in free light chains.

## Management of Cardiac Amyloidosis

The twin aims of management in systemic amyloidosis are: 1) reduction in the supply of amyloid fibril precursor proteins to decrease new amyloid formation and perhaps facilitate the natural regression of existing deposits; and 2) scrupulous general supportive care, including dialysis and organ transplantation in some cases (Fig. 4). Management and prognosis differ substantially in different types of amyloidosis, and accurate fibril typing, frequently including deoxyribonucleic acid analysis, is a prerequisite to optimal care. Unfortunately, the prognosis of cardiac amyloidosis is often very poor at diagnosis, especially in patients with AL type, in whom there may also be significant extracardiac involvement. Awareness of the compromised functional

reserve of amyloidotic organs and extreme care to protect renal function are critically important.

**General supportive care.** The restrictive cardiac physiology and autonomic neuropathy differentiate treatment of CHF in patients with amyloid. The mainstay of the treatment of heart failure in AL amyloidosis is the use of diuretics, with high doses being required in some patients with nephrotic syndrome. Meticulous attention to fluid balance is essential, with daily weights and patient-controlled adjustment of diuretic dose often being helpful. There are no data on the use of beta-blockers in patients with cardiac amyloidosis (59). The restrictive cardiac filling and autonomic neuropathy may lead to severe bradycardia and hypotension, thus limiting their use. Vasoactive drugs, including angiotensin-converting enzyme inhibitors and angiotensin II inhibitors, should be used with caution in cardiac amyloidosis because even small doses may cause profound hypotension. In addition, both digoxin and certain calcium blockers bind to amyloid fibrils, and this



**Figure 4** Flow Diagram Outlining the Evaluation of a Patient With Suspected Cardiac Amyloidosis

BNP = B-type natriuretic peptide; CMR = cardiovascular magnetic resonance; DNA = deoxyribonucleic acid; ECG = electrocardiogram; LV = left ventricle; SAP = serum amyloid P component; TTR = transthyretin.



interaction may account for the increased susceptibility to digoxin toxicity and to hemodynamic deterioration with calcium blockers (60,61). Despite widespread vascular fragility seen in this condition, anticoagulation should not be withheld when cardiac thrombus has been demonstrated within the heart, in atrial fibrillation or when there is sinus rhythm with failure of atrial contraction (62,63).

All manner of arrhythmias have been described in cardiac amyloidosis; the most common of those causing symptoms is atrial fibrillation (64). Although sudden death is frequent in amyloidosis (65), very little is known about the terminal electrical events, and potential benefit of prophylactic antiarrhythmic therapy has been little studied. In our limited experience, electromechanical dissociation is not infrequent. The indications for pacing in cardiac amyloidosis are essentially similar to those in general practice, though concurrent autonomic neuropathy and hypoalbuminemia can substantially exacerbate hypotension-associated poor cardiac output. The threshold for introducing pacing is therefore often lower in patients with amyloidosis, and the restrictive nature of their hemodynamic dysfunction may respond particularly well to dual-chamber systems that can optimize the atrial filling component. Implantable cardiac defibrillators have been used only in a small number of cases. These have not yet been shown to prolong survival, and death is usually due to electromechanical dissociation or congestive heart failure (66). One patient with amyloid cardiomyopathy received a continuous intra-axial cardiac flow pump in the feasibility of long-term continuous axial flow pump study (67). Left ventricular support devices have not been systematically evaluated in patients with cardiac amyloidosis.

**Management of underlying amyloid disease process.** Rational management of the disorders underlying amyloid deposition has been improved greatly by recent availability of routine assays for the circulating amyloid fibril precursor proteins SAA in AA amyloidosis, and serum immunoglobulin free light chains in AL amyloidosis (as described earlier). Treatment of the underlying inflammatory disorder in AA amyloidosis that reduces the SAA concentration toward healthy values dramatically improves survival (6). The new biological agents that inhibit tumor necrosis factor and interleukin-1 potently suppress the acute-phase response in many patients with rheumatoid arthritis, seronegative spondyloarthropathies, Crohn's disease, and some hereditary periodic fever syndromes (68). Treatment with colchicine largely prevents AA amyloidosis in familial Mediterranean fever (69). Excision of solitary Castleman's disease masses that secrete interleukin-6 can be every effective when this condition is complicated by AA amyloidosis (70).

Chemotherapy targeting clonal plasma cells that produce the monoclonal amyloidogenic immunoglobulin light chains can arrest amyloid formation and lead to regression of deposits, preservation of organ function, and enhanced survival in many patients with systemic AL amyloidosis (71,72). Availability of a robust, sensitive immunoassay for

immunoglobulin-free light chains in serum has been one of the most important advances in management of AL amyloidosis. The AL fibril precursor protein can now be monitored prospectively and chemotherapy tailored accordingly in most cases. Sustained reduction of the serum concentration of the aberrant monoclonal light chain value by 50% or more is associated with enhanced survival (72). Unfortunately, many patients with AL amyloidosis tolerate chemotherapy poorly, and a proportion of plasma cell clones are refractory even to high-dose therapy. Oral melphalan and prednisolone are tolerated better than more aggressive treatment, but responses are few and much delayed (73). Intermediate-dose infusional chemotherapy regimens, such as vincristine, adriamycin, and dexamethasone, or melphalan and dexamethasone, which can also be given orally, can induce swifter responses. High-dose chemotherapy coupled with peripheral autologous stem cell rescue (often referred to as stem cell transplantation) has lately been used quite widely, but treatment-related mortality in this setting is 10% to 25%, especially outside specialist amyloidosis centers (23,71). The presence of cardiac amyloidosis is a major determinant of increased morbidity and mortality from peripheral stem cell transplantation (74,75). Cardiac amyloidosis reflects reduced peri-transplant survival compared to those without cardiac involvement. Presence of congestive heart failure, syncope, arrhythmias, renal failure, poor functional status, and involvement of >2 visceral organs predicts a poor outcome and should be excluded for stem cell transplant therapy (75,76). Cardiac involvement, an essential part of screening for stem cell transplantation, may be underestimated by echocardiography. Other approaches currently being explored include thalidomide/lenolidamide alone or in combination chemotherapy (77), rituximab in patients with CD20-positive clones, and new agents including the proteasome inhibitor bortezomib, although no reports exist as to the efficacy of the latter 2 agents. Adequate responses to less intense chemotherapy indicate that high-dose regimens may be excessive, but there is presently no way to identify which individuals will tolerate and respond best to which treatment. The key objective is to sufficiently suppress production of the amyloidogenic free light chain without unacceptable toxicity, and this requires careful individual assessment and monitoring. Interestingly, recent studies using serial measurements of NT-proBNP during chemotherapy suggest that cardiac function in AL can improve rapidly in some cases in association with reduction of the circulating amyloidogenic precursor, despite the amount of cardiac amyloid deposits remaining apparently unaltered on echocardiography (57).

At present, apart from transplantation to replace failed organs and liver transplantation to remove the source of amyloidogenic proteins of hepatic origin, only symptomatic treatment is available in hereditary systemic amyloidosis. The liver is the main source of plasma TTR, and more than 700 liver transplants have been performed in hereditary

TTR amyloidosis since this “surgical gene therapy” approach was introduced in 1991. Outcome is generally good in younger, fitter patients carrying the common Met30 amyloidogenic mutation, but paradoxical acceleration of transthyretin amyloid deposition can occur in the heart following liver transplantation in older patients with non-Met30 variants (78). A few combined heart and liver transplants have been performed, which so far appear to circumvent this predicament.

The livers removed from patients with hereditary TTR amyloidosis contain only microscopic amyloid deposits in the blood vessels and interstitial tissues and retain normal function. A large number of “domino” liver transplants have therefore been conducted in recipients with various terminal liver diseases for whom normal donor livers were not available. This has certainly prolonged their lives, but the first such recipient has now developed symptomatic systemic TTR amyloidosis just 8 years after transplantation (79).

**Cardiac transplantation.** Heart transplantation for cardiac amyloidosis has been performed relatively rarely because of concern about progression of amyloid in other organs and the possibility of amyloid deposition in the donor heart. Twenty-four cases have been performed in the United Kingdom (80). Seventeen patients had AL amyloidosis and 7 had non-AL forms of amyloidosis. Survival of the 10 AL patients who had no adjunctive chemotherapy was 50% at 1 year and 20% at 5 years; amyloid recurred in the grafts of these patients after a median of 11 months, and extracardiac amyloid deposition contributed to mortality in 70% of the patients. Survival of 7 patients with AL who also had chemotherapy was 71% and 36% at 1 and 5 years, with 2 patients alive at 10 years. Survival of the 7 patients with non-AL was 86% and 64% at 1 and 5 years. One such patient with hereditary apoAI amyloidosis had recurrence of amyloid in the graft at 60 months on routine post-transplant biopsies but has no functional deficit after 13 years. Five-year survival for all 24 amyloid patients was 38%, compared with 67% among patients ( $n = 4,058$ ) undergoing cardiac transplantation in the United Kingdom for other indications. Recently, sequential heart and stem cell transplant has shown promise in younger patients complicated with cardiac failure but with preserved renal, gastrointestinal, and autonomic function (81,82). Seventeen patients have been treated with this aggressive approach. Using extended cardiac donor criteria, transplants were performed within 2 months of diagnosis. Induction followed by standard triple-therapy cardiac immunosuppression was continued throughout stem cell transplant. Myeloablative high-dose melphalan was followed by stem cell infusion 6 months after recovery. Sequential transplant patients had a significant survival advantage. Survival at 1 year was 80% versus 17% for nontransplant patients. This was associated with the absence of relapse of plasma cell dyscrasias and allograft rejection. Though the ethical dilemma of offering cardiac

transplant to patients with systemic amyloidosis exists, sequential heart and stem cell transplant offers a feasible strategy for patients with systemic amyloidosis complicated by heart failure.

**Novel therapies.** Elucidation of aspects of the molecular pathogenesis of amyloidosis has generated a variety of novel approaches to therapy. We have developed a drug that targets SAP with the goal of eliminating SAP from amyloid deposits in the hope that this may reduce amyloid deposition and/or accelerate amyloid clearance (83). Preliminary open-label studies are in progress to study safety and tolerability and optimize dosing. Double-blind controlled clinical trials in AA amyloidosis with eprodisate, a small molecule glycosaminoglycan aimed at blocking the pro-amyloidogenic interaction between SAA and glycosaminoglycans, have just been completed. Promising early findings have lately been released (84) for renal disease in AA amyloidosis, further studies on the use of this drug as an adjuvant in AL amyloidosis are warranted, and detailed analysis of outcomes is awaited. Small-molecule ligands that stabilize the native tetrameric structure of TTR and prevent its fibrillogenesis are being actively investigated for prophylaxis and therapy in TTR amyloidosis. Further strategies include stabilizing the native structures of other amyloidogenic proteins and disrupting established deposits using antibodies, synthetic peptides, and small-molecule drugs. Some of these potential new therapies will enter clinical trials within the next few years and offer exciting prospects for improvements in treatment.

## Conclusions

Cardiac amyloidosis describes clinically significant involvement of the heart by amyloid deposition, which may or may not be associated with involvement of other organs. Although no single noninvasive test abnormality is pathognomonic of cardiac amyloid, a combination of a typical echocardiographic appearance and low-voltage ECG complexes is highly suggestive of disease. New imaging techniques such as CMR may offer promise for the early detection of cardiac involvement. In AL amyloidosis, chemotherapy may arrest and even reverse the disease, with resultant stabilization or improvement of symptoms. Thus, early diagnosis is critical because patients with advanced disease are usually too ill for intensive chemotherapy. Cardiac biomarkers, troponin T and I, and NT-proBNP are sensitive markers of cardiac involvement and prognostic determinants. The recent introduction of immunoglobulin light-chain assay is a sensitive marker of response to therapy and survival in AL amyloidosis. Recognition of non-AL cardiac amyloidosis is vital in avoiding unnecessary chemotherapy; to screen family members; and potentially, in the near future, to provide new medications that will stabilize the amyloidogenic protein.



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